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PREPARATION OF LOWER ALDONIC ACIDS BY OXIDATION OF SUGARS IN ALKALINE SOLUTION

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ABSTRACT

Directions are given for the preparation of *l*-erythronic, *d*-threonic, *d*-lyxonic, *l*-xylonic, and *d*-arabonic acids by means of oxidation with oxygen of certain sugars in alkaline solution. *d*-Arabonic acid was obtained in about 70-percent yield, in agreement with the results of prior investigators. Lower yields were obtained for other aldonic acids, and they do not differ greatly from those obtained by oxidation with air. Nevertheless, the simplicity of the method makes it suitable for the production of lower aldonic acids by persons requiring a supply of these scarce materials. *l*-Erythronic and *d*-threonic acids were separated in the form of brucine salts, the optical rotations of which were found to be represented by the following expressions: $[\alpha]_D^{20} = -28.4 - 0.85C + 0.025C^2$, in which *C* is the grams of anhydrous

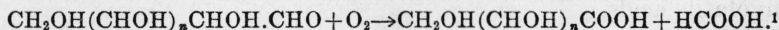
brucine *l*-erythronate in 100 ml of aqueous solution; and $[\alpha]_D^{20} = -28.5 - 0.9C + 0.025C^2$, in which *C* is the grams of anhydrous brucine *d*-threonate in 100 ml of aqueous solution.

CONTENTS

	Page
I. Introduction.....	227
II. Oxidation method.....	228
III. Preparation of brucine <i>l</i> -erythronate from <i>l</i> -arabinose.....	229
IV. Preparation of brucine <i>d</i> -threonate from <i>d</i> -xylose.....	230
V. Conversion of brucine <i>l</i> -erythronate or <i>d</i> -threonate to the corresponding acid.....	231
VI. Preparation of cadmium <i>l</i> -xylonate-cadmium bromide from <i>l</i> -sorbose.....	231
VII. Preparation of <i>d</i> -lyxono- γ -lactone from <i>d</i> -galactose.....	231
VIII. Preparation of calcium <i>d</i> -arabonate from <i>d</i> -glucose.....	232
IX. References.....	232

I. INTRODUCTION

From a study of the oxidation of reducing sugars with air in alkaline solution, Nef and his collaborators [1]¹ found that under the influence of alkali a reducing sugar forms a 1,2-enediol which undergoes oxidation and yields formic acid in addition to an acid containing one less carbon than the parent sugar. The over-all reaction appears to be represented by the following equation:



By using oxygen in place of air, Splengler and Pfannenstiel [2] developed a method for the preparation of potassium *d*-arabonate from dextrose in 60 to 75 percent of the theoretical yield.

¹ Figures in brackets indicate the literature references at the end of this paper.

Subsequently, by essentially the same procedure, Neuberg and Collatz [3] obtained *d*-arabonic-5-phosphoric acid as the barium salt from fructose-5-phosphoric acid in 89-percent yield, whereas Richtermyer, Hann, and Hudson [4] obtained *l*-galactonic acid as the potassium salt from perseulose in 45-percent yield and *d*-altronic acid as the calcium salt from sedoheptulose in approximately 20-percent yield.²

From these publications it was obvious that the oxidation of reducing sugars with oxygen in alkaline solution provides a convenient means for obtaining the lower acids. A supply of *l*-erythronic, *d*-threonic, *l*-xylonic, *d*-lyxonic, and *d*-arabonic acids was needed for other investigations, and hence the preparation of these acids was undertaken by the oxidation of *l*-arabinose, *d*-xylose, *l*-sorbose, *d*-galactose, and *d*-glucose, respectively. Previously, Nef and his collaborators had prepared *l*-erythronic, *d*-threonic, and *d*-lyxonic acids in yields of about 30 percent, by oxidation of *l*-arabinose, *d*-xylose, and *d*-galactose with air in alkaline solution, and it seemed probable that much higher yields might be obtained by the use of pure oxygen. Experiments with oxygen appeared to proceed smoothly, and titrations indicated the production of only slightly more acid than that corresponding to the reaction of eq 1. Nevertheless, it was not possible to separate the desired products in high yield. The simplicity of the process, however, makes it practical for the production of pentonic and tetric acids from sugars which are not very difficult to obtain. The preparation of *l*-xylonic acid from *l*-sorbose is particularly noteworthy, because *l*-xylonic acid can be used as an intermediate in the preparation of ascorbic acid.

II. OXIDATION METHOD

The following procedure was employed for the oxidation of the sugars and for the preparation of the solutions of the nonvolatile acids. In each case 0.05 mole of the sugar was added to 200 ml. of 0.85 *N* potassium hydroxide solution, previously cooled to 0° C, and saturated with oxygen. The solution, in a thick-walled flask, was mixed on a shaking machine with oxygen at a pressure of from 5 to 15 pounds per square inch until the absorption of oxygen ceased (about 24 hours), after which 5 *N* hydrochloric acid was added from a burette in amount equivalent to the potassium hydroxide originally used. The solution was evaporated under reduced pressure to a thin sirup, which was diluted with 50 ml of water and evaporated a second time to substantial dryness to remove all volatile acids. The residue in the flask was digested with 25 ml of hot isopropyl alcohol (99 percent), and cooled to room temperature. After sufficient time for crystallization to take place, the potassium chloride was separated by filtration, washed with hot absolute alcohol, and discarded.³ One gram of decolorizing carbon was added to the alcoholic filtrate and the mixture was given a second filtration to obtain a clear alcoholic solution of the nonvolatile acids.

² A total of 5.1 g of $\text{Ca}(\text{C}_6\text{H}_{11}\text{O}_7)_2 \cdot 3.5\text{H}_2\text{O}$ was obtained from two crude sedoheptulose solutions estimated to contain 10.5 g of sedoheptulose each.

³ In each case the potassium chloride residue was tested to make certain that organic material was not discarded; sometimes a second washing with hot alcohol was necessary.

III. PREPARATION OF BRUCINE *l*-ERYTHRONATE FROM *l*-ARABINOSE

The alcoholic solution of nonvolatile acids obtained from the oxidation of 0.05 mole of *l*-arabinose was mixed with 23 g (0.05 mole) of brucine dissolved in 100 ml of hot 95 percent alcohol. The mixture was placed in a refrigerator and was allowed to stand, with occasional stirring, for 24 hours while crystallization took place. The resulting crystals were collected on a filter and washed with 95 percent alcohol. The air-dried product weighed 17.5 g and melted at 190° to 195° C. The mother liquor was evaporated to a sirup (about 15 ml) which after saturation with isopropyl alcohol gave 3.4 g of crystals with a melting point of approximately 115° C. The second mother liquor gave additional crystals weighing 2.7 g and melting at 205° C. The first crop of material (mp, 190° to 195° C) was heated to boiling with 15 ml of absolute alcohol, and the mixture was cooled and filtered. The crystals on the filter were washed with 10 ml of absolute alcohol, and the filtrate and washings were used to extract the second crop (mp, 115° C), with the result that the melting point was raised to 200° C. The crystalline fractions which remained at this point melted above 200° C and had a combined weight of 18.7 g. By recrystallization from hot ethyl alcohol (600 ml) and concentration of the mother liquors, a total of 13 g of substantially pure brucine *l*-erythronate was obtained.⁴ The yield of brucine *l*-erythronate, 43 percent, was only slightly higher than that obtained by Nef, Hedenberg, and Glattfeld [5] by oxidation of *l*-arabinose with air.

For analysis the material was recrystallized again from hot alcohol and dried at room temperature in air. The substance separates in slender truncated prisms which melt at 212° C and give the following analysis: Calculated for $C_4H_8O_5 \cdot C_{23}H_{26}O_4N_2 \cdot C$, 61.12; H, 6.46. Found: C, 61.38; H, 6.30. The specific rotation in water at a concentration of 4 g per 100 ml of solution was found to be appreciably higher than the value -28.4 reported for brucine *l*-erythronate at the same concentration by Ruff [6] and by Neuberg and Hirschberg [7]. However, by crystallization of the salt from aqueous solution, a product was obtained which gives $[\alpha]_D^{20} = -28.5$. An analysis of this material shows that it is a hydrate with 3.0 moles of water of crystallization.

The hydrated form of brucine *l*-erythronate separates from a concentrated aqueous solution in the form of slender rectangular plates which lose water on heating. The loss in weight when the crystals were heated at 100° C in vacuum was 9.23 percent, whereas the water content of the compound $C_4H_8O_5 \cdot C_{23}H_{26}O_4N_2 \cdot 3H_2O$ is 9.25 percent. The hydrate, when heated slowly, has the same melting point as the anhydrous salt, but when heated rapidly, it melts at a much lower temperature.

Although the existence of the hydrate may account in part for the variation in the values for the optical rotation of brucine *l*-erythronate reported in the literature, some of the variation may have come from failure to take into consideration the concentration of the salt. In 1901, Ruff [6] reported specific rotations of -28.4 and -30.7 at weight concentrations of 4 and 9 percent, but he did not comment on

⁴ In the event that an excess of brucine is present, several recrystallizations are required to obtain the pure salt. Apparently the excess brucine crystallizes with the aldonic acid, perhaps as a basic salt. The excess brucine, if present, can be removed by extraction of an aqueous solution of the salt with chloroform.

the exceptionally large concentration effect. Measurements in the present investigation gave specific rotations of -30.0 , -31.4 , and -34.6 at concentrations of 2, 4, and 10 g per 100 ml. From these values the equation $[\alpha]_D^{20} = -28.4 - 0.85C + 0.025C^2$, in which C is the concentration of the anhydrous salt in water solution, may be calculated to represent the optical rotation of brucine *l*-erythronate. The measurements reported here were made with a polarimeter using a sodium light. It is noteworthy that concentrated solutions of brucine aldones cannot be read satisfactorily with quartz-wedge saccharimeters with the ordinary light source, because the rotatory dispersion of the solution is not satisfactorily compensated by the dispersion of the quartz wedges, and the resulting color effects prevent accurate matching of the saccharimeter field.

IV. PREPARATION OF BRUCINE-*d*-THREONATE FROM *d*-XYLOSE

The alcoholic solution of nonvolatile acids obtained from the oxidation of 7.5 g (0.05 mole) of *d*-xylose was mixed with 23 g (0.05 mole) of brucine dissolved in 100 ml of hot 95 percent alcohol. Crystallization began almost immediately; after 24 hours the crystals were collected on a filter, washed with alcohol, and dried. They weighed 20 g and had a melting point of 207°C and $[\alpha]_D^{20} = -43.7$. By evaporation of the mother liquor, a second crop of crystals weighing 3.2 g was obtained. The second mother liquor on evaporation gave a crystalline residue which melted below 100°C , but failed to give any fractions which appeared to contain brucine *d*-threonate. Inasmuch as both crops of crystals reacted alkaline to litmus, the presence of an excess of brucine was suspected, possibly in the form of a basic salt. To remove the excess brucine, the two crops were combined and dissolved in 100 ml of water, and the aqueous solution was extracted with a total of 150 ml of chloroform in four portions. The chloroform extract was discarded, whereas the water solution was evaporated under reduced pressure to a semifluid crystalline residue which was mixed with 15 ml of isopropyl alcohol. After several hours the resulting crystals were collected on a filter, washed with ethyl alcohol, and dried. The crude product, brucine *d*-threonate, weighed 8.5 g, melted at 210°C , and gave $[\alpha]_D^{20} = -29.4$. In addition to this, 5.3 g of crude brucine *d*-threonate was obtained by concentration of the mother liquors followed by the addition of absolute alcohol.

The yield, approximately 45 percent, is somewhat higher than that obtained by Nef, Hedenberg, and Glattfeld [5] from the oxidation of *d*-xylose with air.

After recrystallization from 30 parts of boiling 95 percent ethyl alcohol and air-drying, anhydrous brucine *d*-threonate was obtained. The anhydrous material melts at 214° to 216°C .

The specific rotation of brucine *d*-threonate⁵ was found to vary widely with concentration; specific rotations of -30.2 , -31.7 , and -35.0 were obtained for aqueous solutions containing 2, 4, and 10 g, respectively, per 100 ml. The equation $[\alpha]_D^{20} = -28.5 - 0.9C + 0.025C^2$ (in which C is the grams of anhydrous salt per 100 ml of water solution) was calculated from these values. This equation is nearly the

⁵ J. U. W. Nef, Liebigs Ann. Chem. **403**, 259, 266 (1914) reported $[\alpha]_D^{20} = -32.4$ (H_2O , $C=4$).

same as that representing the optical rotation of brucine *l*-erythronate. Hence brucine *l*-erythronate and brucine *d*-threonate cannot be distinguished by means of optical rotation measurements. Brucine *d*-threonate on recrystallization from water gave a monohydrate rather than a trihydrate as in the case of brucine *l*-erythronate. Brucine *d*-threonate monohydrate crystallizes in flat rectangular prisms which differ in appearance from the needlelike prismatic crystals of brucine *l*-erythronate trihydrate. The sample of brucine *d*-threonate monohydrate gave the following analysis: Calculated for $C_4H_9O_5 \cdot C_{23}H_{26}O_4N_2 \cdot H_2O$: C, 59.11; H, 6.61; H_2O , 3.28. Found: C, 59.00; H, 6.57; H_2O (loss at $100^\circ C$), 3.16.

V. CONVERSION OF BRUCINE *l*-ERYTHRONATE OR *d*-THREONATE TO THE CORRESPONDING ACID

The brucine salt was converted to the free acid by treating a concentrated aqueous solution of the salt with an equivalent quantity of 0.5 *N* barium hydroxide solution. The brucine set free by the barium hydroxide was extracted from the aqueous solution with chloroform. The aqueous solution containing the barium salt was heated to boiling, and standardized sulfuric acid was added in amount equivalent to the barium hydroxide originally used. The resulting barium sulfate was separated, and the aqueous filtrate was evaporated to dryness. After heating 18 hours at $100^\circ C$, the residue was distilled in high vacuum to yield the crystalline gamma lactone. If seed crystals are available, the distillation can be omitted and the lactone can be separated from the residue by extraction with ethyl acetate. The ethyl acetate solution on the addition of ether yielded the crystalline lactone after seeding.

VI. PREPARATION OF CADMIUM *l*-XYLONATE-CADMIUM BROMIDE FROM *l*-SORBOSE

The alcoholic solution of nonvolatile acids obtained from the oxidation of 9 g (0.05 mole) of *l*-sorbose was evaporated under reduced pressure to a thin sirup, which was diluted with 50 ml of water. The aqueous solution was heated to boiling and digested for 30 minutes with 4.3 g (0.025 mole), of cadmium carbonate and, after the addition of 8.6 g of cadmium bromide tetrahydrate, the resulting solution was filtered. Ethyl alcohol was added to the filtrate until two liquid phases began to appear, whereupon the solution was seeded with cadmium *l*-xylonate-cadmium bromide [8] and was placed in the refrigerator. After 1 day the resulting crystals were separated, washed with aqueous alcohol, and dried in air. The crude cadmium *l*-xylonate-cadmium bromide thus obtained weighed 8 g. Attempts to obtain additional products from the mother liquor were unsuccessful, and the yield of cadmium *l*-xylonate-cadmium bromide, $Cd(C_5H_9O_6)_2 \cdot CdBr_2 \cdot 2H_2O$, was found to be 42.6 percent of the theoretical.

VII. PREPARATION OF *d*-LYXONO- γ -LACTONE [FROM *d*-GALACTOSE

The alcoholic solution obtained from the oxidation of 9 g (0.05 mole) of *d*-galactose was evaporated under reduced pressure to a thick sirup,

which was heated for 18 hours at 100° C. The resulting lactone was dissolved in three 50-ml portions of hot isopropyl alcohol. The alcoholic solution was concentrated to a sirup which was seeded with crystals of *d*-lyxono- γ -lactone. After 2 days, crystallization was substantially complete and the crystals were separated, washed with ethyl acetate, and dried. On evaporation the mother liquor gave additional crystals which were combined with the first crop and were recrystallized from acetone. The resulting product weighed 2.1 g, melted at 114° C, and gave $[\alpha]_D^{20} = +82.7$. These constants are in agreement with those reported by Nef, Hedenberg, and Glattfeld for *d*-lyxono- γ -lactone. The yield, 28 percent, does not differ widely from that obtained by Nef by means of oxidation of *d*-galactose with air.⁶

VIII. PREPARATION OF CALCIUM *d*-ARABONATE FROM *d*-GLUCOSE

The alcoholic solution of nonvolatile acids obtained from the oxidation of 9 g (0.05 mole) of *d*-glucose was evaporated under reduced pressure to a thin sirup, which was diluted with 100 ml of water. The aqueous solution was heated and digested for 30 minutes with 2.5 g of calcium carbonate, and the resulting solution was filtered. Ethyl alcohol was added to the filtrate until two liquid phases began to appear, whereupon the solution was seeded with calcium *d*-arabonate and allowed to stand in the refrigerator. After 1 day the crystals were separated, washed with aqueous alcohol, and dried in air. The crude *d*-arabonate weighed 8 g. After recrystallization from hot water by the addition of alcohol, 7.7 g of pure calcium *d*-arabonate $\text{Ca}(\text{C}_5\text{H}_9\text{O}_6)_2 \cdot 5\text{H}_2\text{O}$ was obtained. This is 67 percent of the yield theoretically possible. The identity of the product was established by conversion to *d*-arabono- γ -lactone.

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⁶J. U. W. Nef, Liebigs Ann. Chem. **403**, 247 (1914), reported 27.4 g of lactone sirup from 100 g of *d*-galactose, which, on further treatment, gave 18.4 g of crystalline *d*-lyxono- γ -lactone. The latter corresponds to a 22-percent yield.